Fruits, Vegetables, and Antioxidants and Risk of Gastric Cancer among Male Smokers

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Abstract

The effect of consumption of fruits, vegetables, and antioxidants on the incidence of gastric cancer is inconclusive. In this prospective cohort study, we report the association of dietary intake of fruits, vegetables, antioxidants, and baseline serum levels of antioxidants with subsequent incidence of gastric cardia cancer (GCC) and gastric noncardia cancer (GNCC). Participants of this study were 29,133 male smokers recruited into the α-Tocopherol, β-Carotene Cancer Prevention study between 1985 and 1988. At baseline, a self-administered food use questionnaire with 276 food items was used to assess dietary intake. Baseline serum samples were stored at −70°C. During a median follow-up of 12 years, 243 incident gastric adenocarcinomas (64 GCC and 179 GNCC) were diagnosed in this cohort, of whom 220 (57 GCC and 163 GNCC) had complete dietary information. For GCC, high dietary intake of retinol was protective [hazard ratio (HR), 0.46; 95% confidence interval (95% CI, 0.27-0.78], but high intake of α-tocopherol (HR, 2.06; 95% CI, 1.20-3.54) and γ-tocopherol (HR, 1.94; 95% CI, 1.13-3.34) increased risk. For GNCC, higher intakes of fruits (HR, 0.51; 95% CI, 0.37-0.71), vitamin C (HR, 0.60; 95% CI, 0.41-0.86), α-tocopherol (HR, 0.78; 95% CI, 0.55-1.10), γ-tocopherol (HR, 0.69; 95% CI, 0.49-0.96), and lycopene (HR, 0.67; 95% CI, 0.47-0.95) were protective. Our results suggest a difference in the effect of some of these exposures on GCC and GNCC. Tocopherols were associated with higher risk of GCC, whereas dietary intake of fruits, vitamin C, tocopherols, and lycopene seemed protective for GNCC. (Cancer Epidemiol Biomarkers Prev 2005;14(9):2087–92)

Introduction

Gastric cancer is the second most frequent cause of cancer death worldwide, claiming >600,000 lives each year (1).

Despite >40 years of epidemiologic research, the effect of high consumption of fruits and vegetables on the incidence of gastric cancer remains controversial. Whereas most retrospective studies have shown that high intake of fruits and vegetables are associated with a moderate reduction in risk of gastric cancer, the results of prospective studies have not shown as strong an effect (2). A recently published meta-analysis found moderate and statistically significant protective effects of fruits and vegetables in case-control studies but only small nonsignificant effects in cohort studies (2).

The protective effect of fruits and vegetables for gastric cancer, if any, has been mainly ascribed to the antioxidant effect of their vitamin contents (2). Some vitamins, such as tocopherols, have antioxidant effects and may reduce the risk of gastric cancer via neutralizing DNA-damaging free radicals generated by various factors, such as chronic *Helicobacter pylori* infection (3, 4). Vitamin C, in addition to its antioxidant effects, reduces N-nitrous compound formation and modifies growth and proliferation of *H. pylori* (5, 6).

One reason for inconsistent results in this area may be failure to analyze results by anatomic subsites in the stomach. Only four prospective studies have evaluated the association between antioxidants and risk of gastric cancer in its main subsites [i.e., gastric cardia cancer (GCC) and gastric noncardia cancer (GNCC); refs. 7-10]. A growing body of evidence suggests that GCC and GNCC may have different etiologic factors (11). For example, the role of *H. pylori* in the etiology of GCC is not clear (12), but it has consistently been shown to be a strong risk factor for GNCC (13). In the past 20 years, the reported incidence of GCC has increased (14-17) or remained constant (18) in the United States and Europe, whereas, during the same period, the incidence of GNCC has dramatically decreased (18).

In this prospective study, we report the association between dietary intake of fruits, vegetables, and select antioxidants and subsequent risk of GCC and GNCC. We also report the effect of baseline serum levels antioxidants on subsequent risk of these cancers.

Materials and Methods

Study Population. The subjects of this study were participants of the α-Tocopherol, β-Carotene Cancer Prevention study. The α-Tocopherol, β-Carotene Cancer Prevention study was a randomized, double-blind, placebo-controlled cancer prevention study launched to examine the hypothesis that α-tocopherol and/or β-carotene supplements reduce the incidence of lung cancer and possibly other cancers. Between 1985 and 1988, 29,133 eligible male smokers ages 50 to 69 years were recruited and randomized to four treatment groups: 50 mg/d α-tocopherol, 20 mg/d β-carotene, both α-tocopherol and β-carotene, or placebo. These participants received daily active supplement or placebo for 5 to 8 years (median, 6.1 years). The study ended in 1993, but the participants are still followed as a cohort. Details of study design and methods have been published elsewhere (19). The conduct of this study was approved by the institutional review boards of both the U.S. National Cancer Institute and the National Public Health Institute in Finland, and all study participants provided written informed consent before the initiation of the study.

Table 1. Median (5th-95th percentiles) of dietary intakes and serum levels of main exposures for the entire cohort, GCC cases, and GNCC cases

	Cohort (n = 27,110)	GCC (n = 57)	P*	GNCC (n = 163)	P*
Age (y)	57 (50-66)	59 (52-67)	<0.001	58 (51-67)	<0.001
Fruits (g/d)	108 (14-291)	111 (29-289)	0.40	94 (0-286)	0.08
Vegetables (g/d)	101 (32-243)	94 (16-248)	0.70	97 (33-226)	0.14
Dietary vitamin C (mg/d)	90 (44-175)	91 (49-178)	0.49	85 (42-168)	0.10
Dietary α-tocopherol (mg/d)	8.5 (5.2-18.2)	10.0 (5.9-19.8)	0.016	7.9 (4.9-20.0)	0.016
Dietary γ-tocopherol (mg/d)	4.8 (0-21.7)	8.0 (0-26.8)	0.015	3.7 (0-25.1)	0.012
Dietary retinol (mg/d)	1.23 (0.54-3.24)	1.03 (0.35-3.14)	0.039	1.11 (0.51-2.98)	0.21
Dietary β-carotene (mg/d)	1.73 (0.65-5.06)	1.56 (0.55-5.16)	0.66	1.75 (0.66-4.34)	0.85
Dietary lycopene (mg/d)	0.63 (0.06-2.11)	0.49 (0.06-2.01)	0.62	0.52 (0.04-1.80)	0.02
Serum α-tocopherol† (mg/L)	11.6 (8.3-16.3)	12.3 (8.6-17.2)	0.09	11.6 (8.0-16.4)	0.97
Serum β-carotene (μg/L)	172 (54-488)	164 (52-452)	0.85	184 (58-469)	0.43
Serum retinol (μg/L)	577 (401-816)	564 (372-817)	0.18	583 (408-809)	0.79

NOTE: All dietary intakes are adjusted for calorie intake using the method of residuals. Median (5th-95th percentiles) of calorie intake were 2,720 (1,706-4,241) kcal in study population.
*Ps have been calculated using Wilcoxon rank-sum test.
†Serum α-tocopherol is adjusted for serum cholesterol level. Median (5th-95th percentiles) of serum cholesterol were 6.15 (4.49-8.26) mmol/L in study population.

Data Collection. At study entry, all participants completed a questionnaire on general background characteristics and habits, and each gave a fasting serum sample, which was stored at −70°C. Diet was assessed using a self-administered food use questionnaire with 276 food items and mixed dishes aided by a portion size picture booklet with 122 photographs (20). Each participant was asked to report the usual frequency of consumption and the usual portion size of foods during the previous 12 months. The food frequency questionnaire was satisfactorily completed by 27,110 participants (93%) at baseline. Dietary intake of nutrients was calculated by use of the software and food composition data available at the National Public Health Institute of Finland.

The dietary questionnaire was compared with food records in a separate validity study of 190 middle-aged men, and the reproducibility of vitamin assessment was studied in 121 men who completed the food use questionnaire thrice at 3-month intervals. Correlations between nutrient intake values from the food records and the food use questionnaire ranged from 0.41 for vitamin A to 0.64 for vitamin E. The intraclass correlations from the three food use questionnaires varied from 0.56 for vitamin A to 0.70 for vitamin E (20).

Serum α-tocopherol, β-carotene, and retinol concentrations were determined by high-performance liquid chromatography assay. The between-run coefficients of variation were 2.2% for α-tocopherol, 3.6% for β-carotene, and 2.4% for retinol (21).

Gastric Cancer Ascertainment. The cases in this study were incident gastric adenocarcinomas diagnosed since randomization through April 30, 1999. Incident cancer cases were primarily identified via the Finnish Cancer Registry, which provides ~100% case coverage (22). Diagnosis of gastric cancer cases (*International Classification of Diseases, Ninth Edition* code 151) was confirmed by review of hospital records and histopathologic specimens. The review also included assignment of anatomic subsite within the stomach as GCC (n = 64) or GNCC (n = 179) cases. GCC cases were defined as those cases in whom the cancer involved the esophagogastric junction.

Statistical Analysis. Medians and 5th and 95th percentiles for each variable of interest were calculated for the entire cohort, GCC cases, and GNCC cases. We used the Wilcoxon rank-sum test to compare the distribution of variables of interest in GCC and GNCC patients versus the other members of the cohort. We used Cox proportional hazards model to estimate the association between our variables of interest and the risk of GCC and GNCC, adjusting for confounders. Our variables of interest included baseline dietary intake of fruits, vegetables, vitamin C, α-tocopherol, γ-tocopherol, retinol, β-carotene, and lycopene as well as baseline serum concentrations of α-tocopherol,

β-carotene, and retinol. The dietary intakes were adjusted for total energy intake using the method of residuals (23). Serum α-tocopherol was adjusted for total serum cholesterol. A preliminary list of confounders was prepared based on existing literature. This list included age (years), level of education (primary and less versus more), total smoking duration (years), consumption of alcohol (g/d), dietary intake of sodium (mg/d), nitrates and nitrites (mg/d), vitamin A or β-carotene supplementation (yes/no), and treatment group (α-tocopherol, β-carotene, both, or placebo). The final list of confounders was selected based on a change of >10% in β coefficients in Cox regression analyses.

Using data from the entire cohort, we classified our variables of interest into quartiles. To evaluate the association between our variables of interest and the risk of GCC and GNCC, we used three methods. First, we estimated hazard ratio (HR) and their 95% confidence intervals (95% CI) separately within each quartile. Second, we used the quartile score as an ordinal variable (0-3) to perform the Cuzick trend tests. Third, based on quartile score, we did the P global (3 df) tests to determine whether there is a risk difference between quartiles without assuming any linear progression. Where we observed a two-sided P for trend ≤ 0.05 and also a clear pattern of association, we conducted a *post hoc* test. We assumed that some dietary factors may become harmful when taken in excessive amounts and others when not taken in adequate amounts. Therefore, as a rule, we selected the extreme cut points for *post hoc* analyses (i.e., we chose quartile 1 for factors associated with a reduced risk and quartile 4 for factors associated with an increased risk).

Follow-up time was computed as the time since the start of the intervention until the date of diagnosis (cases), the date of death, or the end of the present follow-up (April 30, 1999), whichever came first. The assumption of proportional hazards was verified in all analyses. Throughout the article, all Ps are two sided.

Results

Of the 256 gastric cancer cases diagnosed by April 30, 1999, 243 (95%) were gastric adenocarcinomas (64 GCC and 179 GNCC cases). Among adenocarcinoma cases, 220 (57 GCC and 163 GNCC) had complete dietary information. Only gastric adenocarcinomas with complete dietary information were included as cases in this study. Table 1 shows median and 5th and 95th percentiles of age and main exposures of this study for GCC cases, GNCC cases, and the entire cohort. At study entry, the entire cohort had a median age of 57 years and

median smoking duration of 36 years (35 pack-years). Twenty-one percent of the entire cohort had education above the primary level. Median dietary intakes of vitamin C, α-tocopherol, γ-tocopherol, retinol, and β-carotene in the entire cohort were 90, 8.5, 4.8, 1.2, and 1.7 mg/d, respectively. Median serum concentrations of α-tocopherol, β-carotene, and retinol in the entire cohort were 11.6 mg/L, 172 μg/L, and 577 μg/L, respectively.

Table 2 shows the HRs and 95% CIs for the association of fruits, vegetables, and antioxidants and the risk of GCC and GNCC. Higher intake of fruits did not alter the risk of GCC but decreased the risk of GNCC (P for trend < 0.001). Our data suggest that low levels of fruit intake (≤61 g/d or below the first quartile) were associated with higher risk of GNCC; moderate to high intake of fruits (≥61 g/d) reduced the risk by about half (HR, 0.51; 95% CI, 0.37-0.71). We did not find a clear pattern of association between vegetable intake and risk of either GCC or GNCC.

Intake of vitamin C was not associated with the risk of GCC, but moderate to high intake of vitamin C (≥69 mg/d or above the first quartile) was associated with a 40% reduction in the risk of GNCC (HR, 0.60; 95% CI, 0.41-0.86). There was a strong correlation between intake of vitamin C and fruits (Pearson's r = 0.79), which explains why vitamin C intake and fruit intake showed similar results.

Higher consumption of α-tocopherol was associated with an increased risk of GCC in a dose-dependent manner (P = 0.01; Table 2). Intake of >11.5 mg/d (the highest quartile) increased the risk of GCC by 2-fold (HR, 2.06; 95% CI, 1.20-3.54). Higher intake of α-tocopherol was associated with a progressive and significant reduction in GNCC risk (P = 0.01). However, a post hoc test comparing moderate or high (≥6.9 mg/d) versus lower showed a nonsignificant association (HR, 0.78; 95% CI, 0.55-1.10). Baseline serum values of α-tocopherol were not significantly associated with the risk of GCC or GNCC, but the association between serum levels and GCC paralleled that of dietary intake (Table 3). The correlation coefficient between dietary intake and serum level of α-tocopherol was 0.36, showing only a modest degree of association between these two measures.

γ-Tocopherol was associated with a higher risk of GCC (P = 0.03) but a lower risk of GNCC (P = 0.01). Dietary intake of γ-tocopherol at ≥10.0 (vs. <10) was associated with a 2-fold increased risk of GCC (HR, 1.94; 95% CI, 1.13-3.34). Conversely, intake of γ-tocopherol higher than 2.0 mg/d (above the first quartile) decreased the risk of GNCC by about one third (HR, 0.69; 95% CI, 0.49-0.96).

Intake of retinol had a dose-dependent protective association with GCC (P = 0.04) but was not associated with the risk of GNCC (Table 2). Intake of ≥0.88 mg/d retinol (above the first quartile) decreased the risk of GCC by over half (HR, 0.46; 95% CI, 0.27-0.78). Patterns of associations between serum retinol and GCC and GNCC were similar to dietary intake but weaker and nonsignificant (Table 3).

Neither dietary intake nor serum levels of β-carotene were associated with the risk of either GCC or GNCC (Tables 2 and 3).

Dietary lycopene did not have a significant effect on the risk of GCC but had a significant protective effect for GNCC (P = 0.01). Lycopene intake of >0.3 mg/d (above the first quartile) was associated with a one-third reduction in the risk of GNCC (HR, 0.67; 95% CI, 0.47-0.95).

Discussion

This study is one of the few prospective studies that have considered the association between antioxidants and anatomic subtypes of gastric cancer (GCC and GNCC). Numerous differences in dietary risk factors were seen for these subsites. Intakes of fruits and vitamin C were not associated with the risk of GCC but were inversely associated with the risk of GNCC. Higher intakes of both α-tocopherol and γ-tocopherol increased the risk of GCC but decreased the risk of GNCC. Higher intake of dietary retinol decreased the risk of GCC but had no effect on the risk of GNCC. Dietary lycopene was not protective for GCC but showed a significant protective association with GNCC.

At least 11 prospective studies and 30 retrospective studies have reported on the association between intake of fruits and vegetables and the risk of gastric cancer. However, the effect of

Table 2. HRs and 95% CIs for the association of dietary intakes of fruits, vegetables, and antioxidants and the risk of GCC (n = 57) and GNCC (n = 163)

	Quartile1	Quartile2	Quartile3	Quartile4	P for trend*	Global P†
Fruits (g/d)	≤61	62-107	108-166	≥167		
GCC	1.00	0.93 (0.44-1.97)	0.84 (0.39-1.83)	1.00 (0.47-2.18)	0.77	0.96
GNCC	1.00	0.41 (0.26-0.65)	0.50 (0.32-0.78)	0.66 (0.43-1.02)	0.04	<0.001
Vegetables (g/d)	≤66	67-100	101-147	≥148		
GCC	1.00	1.52 (0.74-3.10)	0.44 (01.6-1.22)	0.81 (0.27-2.48)	0.59	0.04
GNCC	1.00	0.94 (0.60-1.45)	0.85 (0.51-1.40)	0.85 (0.43-1.68)	0.11	0.45
Dietary vitamin C (mg/d)	≤68	69-89	90-117	≥118		
GCC	1.00	0.77 (0.36-1.68)	0.90 (0.41-1.95)	1.00 (0.42-2.36)	0.77	0.89
GNCC	1.00	0.58 (0.37-0.90)	0.54 (0.34-0.87)	0.77 (0.47-1.26)	0.05	0.01
Dietary α-tocopherol (mg/d)	≤6.8	6.9-8.4	8.5-11.4	≥11.5		
GCC	1.00	0.72 (0.29-1.80)	1.44 (0.64-3.21)	2.18 (1.03-4.62)	0.01	0.04
GNCC	1.00	0.84 (0.56-1.27)	0.83 (0.54-1.30)	0.63 (0.40-1.02)	0.01	0.09
Dietary γ-tocopherol (mg/d)	≤2.0	2.1-4.7	4.8-9.9	≥10.0		
GCC	1.00	0.91 (0.38-2.14)	1.34 (0.60-3.02)	2.11 (1.00-4.45)	0.03	0.13
GNCC	1.00	0.62 (0.40-0.95)	0.85 (0.56-1.29)	0.61 (0.39-0.96)	0.01	0.02
Dietary retinol (mg/d)	≤0.87	0.88-1.23	1.24-1.90	≥1.91		
GCC	1.00	0.40 (0.19-0.84)	0.58 (0.39-1.12)	0.41 (0.19-0.86)	0.04	0.05
GNCC	1.00	1.00 (0.66-1.53)	0.98 (0.64-1.50)	0.78 (0.49-1.24)	0.24	0.40
Dietary β-carotene (mg/d)	≤1.14	1.15-1.72	1.73-2.65	≥2.66		
GCC	1.00	1.31 (0.65-2.63)	0.50 (0.20-1.23)	0.85 (0.35-2.05)	0.59	0.15
GNCC	1.00	0.89 (0.57-1.40)	0.99 (0.61-1.58)	1.33 (0.80-2.22)	0.86	0.68
Dietary lycopene (mg/d)	≤0.31	0.32-0.62	0.63-1.07	≥1.08		
GCC	1.00	1.29 (0.62-2.68)	1.06 (0.48-2.33)	0.97 (0.41-2.34)	0.85	0.86
GNCC	1.00	0.58 (0.37-0.90)	0.80 (0.53-1.23)	0.62 (0.37-1.03)	0.01	0.01

NOTE: All HRs are adjusted for the effects of age, total years of smoking, education, and dietary nitrate.
*Derived from the Cuzick trend test.
†Derived from the 3 df test for the overall quartile model.

Table 3. HRs and 95% CIs for the serum levels of antioxidants and the risk of GCC (*n* = 57) and GNCC (*n* = 163)

	Quartile1	Quartile2	Quartile3	Quartile4	*P* for trend*	Global *P*†
Serum α-tocopherol (mg/L)	≤10.3	10.4-11.5	11.6-13.1	≥13.2		
GCC	1.00	1.67 (0.72-3.87)	1.54 (0.66-3.58)	2.21 (0.99-4.93)	0.07	0.24
GNCC	1.00	0.99 (0.64-1.55)	1.01 (0.66-1.58)	1.14 (0.74-1.77)	0.94	0.98
Serum retinol (μg/L)	≤501	502-575	576-661	≥662		
GCC	1.00	0.82 (0.42-1.62)	0.56 (0.26-1.21)	0.75 (0.37-1.54)	0.17	0.38
GNCC	1.00	0.85 (0.54-1.33)	1.14 (0.76-1.75)	0.94 (0.60-1.48)	0.66	0.45
Serum β-carotene (μg/L)	≤110	111-172	173-261	≥262		
GCC	1.00	1.00 (0.49-2.09)	0.95 (0.45-2.00)	0.92 (0.44-1.95)	0.92	0.99
GNCC	1.00	1.03 (0.66-1.63)	1.25 (0.81-1.94)	1.05 (0.67-1.67)	0.57	0.58

NOTE: All HR are adjusted for the effects of age, total years of smoking, education, and dietary nitrate.
*Derived from the Cuzick trend test.
†Derived from the 3 *df* test for the overall quartile model.

high consumption of fruits and vegetables on the incidence of gastric cancer remains controversial. A recent meta-analysis of cohort studies showed a nonsignificant and small protective association: the summary RRs (95% CIs) for fruits and vegetables were 0.89 (0.73-1.09) and 0.89 (0.75-1.05; ref. 2). Whereas the results of cohort studies exploring the association between fruits and vegetables and the risk of gastric cancer have not been entirely consistent, with the exception of one small study (24), all other cohorts have suggested that intake of fruits and vegetables are slightly protective for gastric cancer, with risk point estimates typically between 0.5 and 1.0 (8, 25-30). Our study suggests a protective effect of fruits and a small or null effect of vegetables for GNCC (the major site of gastric cancer in other studies).

In our study, higher intake of vitamin C had a significant protective association with GNCC. Because intake of vitamin C was highly correlated with intake of fruits, this protective effect was expected. Other studies have also consistently shown that vitamin C is protective for gastric cancer (31-34), most notably for GNCC (35, 36).

Vitamin E has long been suggested to reduce the risk of cancer via its antioxidant effects (37). There are, however, some indications that vitamin E may accelerate late carcinogenesis by inhibition of apoptosis (38). Vitamin E occurs in eight structurally related forms, the two most important of them being α-tocopherol and γ-tocopherol (39). Previous cohort studies have shown inconsistent results for the associations between α-tocopherol and risk of gastric cancer, showing no association with dietary intake of α-tocopherol (32), no association with dietary supplements of vitamin E (40), an increase in gastric cancer risk with higher baseline serum level of α-tocopherol (34), and increased risk only in GNCC but not in GCC (10).

It was possible to evaluate the association of α-tocopherol and future risk of GCC and GNCC in the α-Tocopherol, β-Carotene Cancer Prevention study cohort in three ways using (*a*) interventional supplementation with α-tocopherol, (*b*) baseline dietary intake of α-tocopherol, and (*c*) baseline serum levels of α-tocopherol (41). The results of these three methods (intervention, intake, and serum level) were not completely concordant. A previous study on the α-Tocopherol, β-Carotene Cancer Prevention cohort showed that interventional supplementation with α-tocopherol did not change the risk of GCC (HR, 1.00; 95% CI, 0.47-2.13) but slightly and nonsignificantly increased the risk of GNCC (HR, 1.27; 95% CI, 0.85-1.89; ref. 41). In this study, higher dietary intake of α-tocopherol was associated with a higher risk of GCC but a slight and nonsignificant reduced risk of GNCC. Baseline serum concentrations of α-tocopherol were not significantly associated with the risk of either GCC or GNCC. Although there was a similar trend toward higher risk of GCC with increasing serum α-tocopherol as with dietary α-tocopherol, we cannot fully reconcile these divergent results; each of these methods has its

own advantages and disadvantages. Intervention results apply only to the dose and duration of supplementation given and the population supplemented. However, we can conclude that there is little evidence of benefit from intervention with α-tocopherol in preventing gastric cancer in later years of life. Although dietary intake measurements may reflect long-term consumption, they may also have considerable measurement errors or be strongly confounded by other unaccounted factors. Serum levels of α-tocopherol show its concentration at only one point in time, may not necessarily represent tissue levels, and may also suffer from measurement errors.

γ-Tocopherol is the major form of vitamin E in the U.S. diet, but it has received less attention than α-tocopherol, mainly because of its lower bioavailability and bioactivity (39). However, it has been suggested that γ-tocopherol has unique features important to human health that are not shared with α-tocopherol (39). For example, γ-tocopherol seems to be more effective than α-tocopherol in trapping lipophilic electrophiles (39) and in inhibiting cell cycle progression and cell proliferation (42). To our knowledge, only one study has examined the association of serum γ-tocopherol with the risk of gastric cancer and that case-cohort study found no association between baseline serum levels of γ-tocopherol and the risk of GCC (RR, 0.97) or GNCC (RR, 1.00; ref. 10). In contrast, our results suggest an increased risk of GCC and a decreased risk of GNCC associated with baseline intake of γ-tocopherol. An elevated risk of cancer among individuals with a high intake of tocopherols (including both α-tocopherol and γ-tocopherol) may be due to biological effects, such as inhibition of apoptosis, or may be due to confounders, such as unmeasured carcinogens in the dietary sources of tocopherols. An example of such a confounding carcinogen is cooking oil, which is both a source of tocopherols and a potential risk factor for gastric cancer (30). Margarines, eggs, butter, and grains were the main sources among the participants of α-Tocopherol, β-Carotene Cancer Prevention.

Interestingly, tocopherols had a dual effect on risk of gastric cancer; they were associated with a higher risk of GCC but a lower risk of GNCC. However, persons with a moderate intake of tocopherols (7-11 mg/d α-tocopherol and 2-10 mg/d γ-tocopherol) showed a lower risk of GNCC without suffering from an increased GCC risk.

The two major sources of dietary vitamin A are retinyl esters and carotenoids, most notably β-carotene (43). Most prospective observational studies have not found any effect of serum levels (25, 44) or dietary intake (14) of retinol on the risk of gastric cancer. Only one prospective study has explored the association of serum retinol with the risk of GCC and GNCC separately; this study found that higher serum retinol significantly decreased the risk of GCC but was not associated with the risk of GNCC (9). Consistent with this study, our results indicate that both serum levels and dietary intake of retinol are associated with a decreased risk of GCC but not

with GNCC. Our results strengthen the evidence in favor of anticarcinogenic effects of retinoids (3).

The association of β-carotene with gastric cancer is controversial. Whereas some prospective studies have shown an inverse association between serum levels of β-carotene and the risk of gastric cancer (25, 44), others have not found such an association for either serum levels (9) or dietary intake (14) of β-carotene. As with α-tocopherol, we were able to evaluate the association of β-carotene and subsequent risk of GCC and GNCC in three ways. Our previous study showed that interventional supplementation with β-carotene nonsignificantly increased the risk of GCC (HR, 1.81; 95% CI, 0.82-3.98) and did not change the risk of GNCC (HR, 1.13; 95% CI, 0.76-1.46; ref. 41). In this study, we did not find an association between dietary intake or serum levels of β-carotene and the risk of either GCC or GNCC.

Lycopene has been shown to have antioxidant effects and to reduce the risk of gastric cancer in animal models (45). Case-control studies have shown an inverse association between intake of tomatoes or lycopene and the risk of gastric cancer (46, 47). To our knowledge, this is the first prospective study that has assessed the association of lycopene intake and risk of gastric cancer. Lycopene did not affect the risk of GCC but seemed to decrease the risk of GNCC by ~33%. These results support the existing evidence that lycopene may be a useful chemopreventive agent for the prevention of gastric cancer.

Strengths of this study include its prospective design, large sample size, long-term and complete follow-up, completeness, and accuracy in measurement of dietary exposures and confounders. There are, however, some limitations to this study. Most notably, there may be a possible misclassification in subtypes of gastric cancer within our data, as differentiating adenocarcinomas arising in the gastric cardia from those arising in the lower esophagus or the body of the stomach is not always possible. Because our assessment of the cancer location was done retrospectively based on clinical records, the site of origin could not always be accurately determined. Thus, we defined cardia cases as those in which the cancer involved the esophagogastric junction. This problem, however, is also common in most other studies of etiologic factors of cardia cancers. In parts of Asia, such as Linxian, China, Barrett's esophagus and adenocarcinomas of the lower esophagus are virtually nonexistent, so the tumors classified as cardia cancers in such areas are less heterogeneous and thus may be different from those recorded in Western studies. This difference in definition may explain some of the differences found between our results and those seen in studies conducted in China. Finally, we have done some *post hoc* analyses. To avoid an increase in type I error, *post hoc* analyses were done only when the *P* for trend was ≤0.05 and a clear pattern of association was observed. In addition, cut points for *post hoc* tests were predefined as the lowest quartile for protective associations and the highest quartile for harmful associations. However, the results of these *post hoc* analyses should be taken with caution.

In summary, we showed that the effects of some of these nutritional agents on the risk of GCC and GNCC are different, suggesting that these two types of cancer should be studied separately wherever possible. For GCC, higher dietary intake of retinol was protective, but dietary intake of α-tocopherol and γ-tocopherol increased risk. For GNCC, higher intakes of fruits, vitamin C, tocopherols, and lycopene were protective.

Acknowledgments

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